REMARKS/ARGUMENTS

After entry of this amendment, claims 13-18, 28-32, and 69-71 are pending in the present application. Claim 13 is amended to be independent and incorporate the limitations of claim 3, from which it depended. Claim 15 is amended to be independent and incorporate the limitations of claim 4, from which it depended. Claims 17 and 18 are amended to be dependent from claims 13 and 15, respectively. Claims 28-32 have been amended to be dependent from claims 13 or 15. New claims 69-71 correspond to cancelled claims 10-12, respectively. No new matter is added by this amendment.

Rejections under 35 U.S.C. § 112, second paragraph

The rejection of the claims 1, 5, 7, 19, 28 and 30 for use of the terms "native" and "variant" is rendered overcome in part by cancellation of claims 1, 5, 7, and 19, and is respectfully traversed in part, as explained below. The rejection of claims 28-32 for being duplicates of claims 5-9 is rendered moot by cancellation of claims 5-9.

In the Office Action, the Examiner asserts that claims 28 and 30 are indefinite because the definitions of "native AAT" and "variant AAT" allegedly overlap. As explained in paragraph [0020] of the specification, the term "AAT" refers to proteins having the native AAT sequence, as well as variants of the sequence ***"regardless of origin or mode of preparation"*** (*see* page 4, lines 14-16). Thus, this term encompasses both naturally occurring and recombinant forms.

Encompassed within the broad genus of AAT proteins are those that are referred to as "naturally occurring" or "native" AAT, which are defined to be AAT forms ***"isolated from natural sources"*** (*see* page 4, lines 19-20). These terms encompass a wide variety of naturally occurring variants, including naturally occurring truncated or soluble forms, alternatively spliced variants, allelic variants, posttranslational variants, and the like (*see* page 4, lines 21-23).

Another subgenus of AAT proteins are "AAT variants," which as explained in paragraph [0021] are ***"functional equivalents to"*** native AAT, but are not themselves native AAT proteins, as defined above. Thus, unlike native AAT proteins, "AAT variants" are not isolated from natural sources and are therefore not naturally occurring proteins.

In view of the above, Applicants respectfully submit that the two terms encompass two different classes of AAT proteins that do not overlap. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-32 stand rejected for allegedly lacking enablement. In the Office Action, the Examiner acknowledges that the claims are enabled for functional AAT proteins (*e.g.*, wild type AAT) which are serine protease inhibitors, but rejects the claims to the extent they read on AAT protein variants that lack this function. To expedite prosecution and without further limiting the pending claims, Applicants have amended the claims to clarify that the AAT used in the claimed formulations are functional. Support for this amendment is replete throughout the specification, which describes the invention as directed to, among other things, stable formulations of AAT for use as a therapeutic (*see e.g.*, first paragraph of the Summary of the Invention, paragraph [0009]).

In the Office Action, the Examiner further takes the position that determining whether a particular AAT variant retains the function of native AAT proteins would require undue experimentation. To the extent this rejection is maintained in spite of the above claim amendments, Applicants respectfully traverse.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. *See*, M.P.E.P. § 2164.01, *citing United States v. Telectronics, Inc.*,857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

In the present case, as is explained in the Background Section of the Application, AAT is a well-characterized protease inhibitor used extensively to treat patients with genetic disorders that lead to AAT deficiency. Specific examples of native AAT sequences are available from GenBank as well as the patent literature (*see* page 4, lines 24-26, and US Patent Nos. 4,599,311 and 4,711,848). In addition, recombinant AAT proteins have been described (*see* page 4, lines 27-31, and US Patent Nos. 4, 599,311, 4,931,373, and 5,218,091). Suitable variant AAT proteins are also described, for example, in paragraph [0025]on page 5 (*e.g.*, US Patent Nos. 4,732,973 5,134,119, and 4,711,848). The specification further describes well-known means for preparing additional variants (*see* paragraph [0023] on page 5) and for testing the function of the variants produced by these methods (*see* paragraph [0075] on page 15).

Thus, the disclosure provides abundant evidence of exemplary AAT sequences, including both naturally occurring and engineered variants, that could be used in the claimed formulations. The specification further described means for preparing and testing additional variant using well-known techniques. In view of the above, one of skill could make and use a variety of functional AAT proteins without undue experimentation. The present rejection is therefore improper and should be withdrawn.

Rejections under 35 U.S.C. § 102(b)

The rejection of claims 19, 20, 22, and 28-30 for allegedly being anticipated by US Patent No. 5,618,786 and claims 1-7, 10-12, and 28-30 for allegedly being anticipated by US Patent No. 6,267,958, are rendered moot by the above amended claims. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

The rejection of claims 8-9, 13-27, and 31-32 for allegedly being obvious over the '958 patent in view of US Paten No. 5,166,134 and the '786 patent is respectfully traversed.

The '958 patent is cited for allegedly teaching a lyophilized composition comprising a protein, a carbohydrate, a surfactant and an antioxidant. AAT is included in the reference among a long list of proteins that could potentially be used in the compositions disclosed there. As noted by the Examiner, the only actual data for stable protein compositions

involve a completely unrelated protein (HER2 antibody). The '134 patent is cited for allegedly teaching AAT at 0.1-4.5% w/v in an aqueous solution. The Examiner points to nothing in this reference, however, relating to the other components of the claimed compositions. Finally, the Examiner cites the '786 patent for teaching aerosol AAT formulations comprising a carbohydrate and a surfactant. Again, the Examiner cites to nothing in this reference that discloses or suggests the use of antioxidants, as claimed here.

It is well settled that the Examiner has the burden of presenting a *prima facie* case of obviousness. Analysis of obviousness under 35 U.S.C. § 103(a) requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. Indeed, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *See*, *KSR Int'l Co. v. Teleflex Inc.*, 500 U.S. 398, 418 (2007), quoting *In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006). Moreover, the rationale must show that one of skill would have had a reasonable expectation of success. MPEP §2143.02.

In the present case, the Examiner cites a collection of prior art references that each disclose some, but not all, of the components of the claimed compositions. Based on these disclosures, the Examiner simply asserts that the particular claimed compositions are obvious with out articulating any reasoning or providing any evidence to show why one of skill would be led to the claimed invention based on these disclosures. In view of the case law noted above, the rejection is improper and should be withdrawn.

In addition, the Examiner does not properly address the limitations recited in claims 13 and 14 relating to the concentration ranges of each of the components in the claimed compositions. There is no analysis showing how the claimed concentration ranges are met by any of the cited references. Instead, the Examiner simply asserts that "[i]t reasonably appears that the ranges for carbohydrate and surfactant concentrations taught by the prior art meet the limitations of the instant claims." (*see* Office Action, page 6, lines 19-21). Applicants respectfully submit that this does not provide the proper articulated reasoning and rational

underpinning to support the Examiner's legal conclusion of obviousness, as required under the law noted above.

In conclusion the Examiner has not addressed the teachings missing from the cited references and failed to show why one of skill would combine the cited references in the manner suggested. In addition, the Examiner has not provided sufficient reasoning or evidence to show what in the art would lead one of skill to the concentration ranges recited in the pending claims. In the absence of a proper showing in both of these regards, the rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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